Limits: **Publication Date to 1995/06/07**

1: J Immunol. 1993 Feb 1;150(3):1036-46.

T lymphocytes capable of activating endothelial cells in vitro are present in rats with autoimmune diabetes.

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Department of Medicine, University of Massachusetts Medical Center, Worcester 01655.

Endothelial activation as evidenced by increased expression of leukocyte adhesion molecules occurs during immune-mediated inflammatory processes One such process is insulitis, the pancreatic islet inflammation that leads to autoimmune insulin-dependent diabetes mellitus (IDDM). To determine if th induction of IDDM correlates with the presence of T lymphocytes capable of activating endothelial cells (EC), we studied the diabetes resistant BB (DR) r These animals become diabetic after in vivo depletion of T cells expressing t RT6 alloantigen. Various populations of purified DR T lymphocytes were cocultured with MHC compatible rat EC. We observed: 1) RT6- T cells from diabetic animals induced maximal endothelial MHC Ag expression. 2) The ability of RT6- T cells to activate EC increased with the duration of in vivo RT6 depletion. It was acquired before the onset of insulitis but subsided after the onset of diabetes. 3) In contrast, neither unsorted total T cells nor in vitro purified RT6- T cells activated EC. 4) Older DR rats depleted of RT6+ T cel did not become diabetic and their RT6- T cells did not activate EC. 5) T cell IFN-gamma production correlated with the intensity of EC activation. 6) dire T cell-EC contact was required for maximal IFN-gamma production and EC activation. We conclude that RT6- T cells capable of activating EC are generated during the induction of IDDM in DR rats. We hypothesize that suc T cell activity may lead to endothelial activation in vivo and contribute to immune-mediated insulitis, beta-cell destruction, and IDDM.

PMID: 8423330 [PubMed - indexed for MEDLINE]

1: Diabetologia. 1994 Jan;37(1):22-31. Related Articles, Li

Reactive oxygen intermediates in autoimmune islet cell destruction of the NOD mouse induced by peritoneal exudate ce (rich in macrophages) but not T cells.

Horio F, Fukuda M, Katoh H, Petruzzelli M, Yano N, Rittershaus C, Bonner-Weir S, Hattori M.

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The non-obese diabetic (NOD) mouse spontaneously develops autoimmune Type 1 (insulin-dependent) diabetes mellitus. NOD mice exhibit massive infiltrates of T cells and macrophages into pancreatic islets (insulitis) prior to diabetes. The contribution of oxygen free radicals to the development of insulitis in NOD mice was examined by administration of its scavengers, suc as superoxide dismutase and catalase. Bovine superoxide dismutase and catalase were each coupled to polyethylene glycol. The treatment with superoxide dismutase-polyethylene glycol reduced the number of islets with insulitis and increased the undamaged islet tissue, as compared with the cont group. The treatment with catalase-polyethylene glycol showed a similar tendency which did not reach significance. Using a flow cytometric assay of the oxidation of 2', 7'-dichlorofluorescein, the content of reactive oxygen intermediates in islet cells in the culture system was measured and the effect peritoneal exudate cells and T cells on their production examined. Peritoneal exudate cells, but not T cells, from NOD mice increased the content of reacti oxygen intermediates in islet cells of either the NOD mouse or the ILI mouse (MHC-identical to NOD); the addition of superoxide dismutase to the culture medium suppressed this increase in NOD or ILI islet cells. The present data support the concept that production of oxygen free radicals mediated by macrophages can damage islet beta cells, directly resulting in autoimmune Type 1 diabetes in NOD mice.

PMID: 8150225 [PubMed - indexed for MEDLINE]

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1: Diabetes. 1994 May;43(5):613-21.

Comment in:
- Diabetes. 1995 Jul;44(7):859-62.

Immunoregulatory and cytokine imbalances in the pathogenesis of IDDM. Therapeutic intervention by immunostimulation?

Rabinovitch A.

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The autoimmune response that leads to destruction of pancreatic islet beta-ce and insulin-dependent diabetes mellitus (IDDM) has a genetic basis; howeve environmental factors can exert profound modulating effects on the genetic predisposition to this autoimmune response. Recent studies in animal models for human IDDM, the genetically diabetes-prone NOD mouse and BB rat, ha revealed that microbial agents--including certain viruses and extracts of bacteria, fungi, and mycobacteria--often have a protective action against diabetes development. Many of these microbial preparations are immune adjuvants, which are agents that stimulate the immune system. The protectiv effects of these agents against diabetes appear to involve perturbations in the production of cytokines, which are polypeptides produced by and acting on cells of the immune system. Thus, recent studies in NOD mice suggest that tl islet beta-cell-directed autoimmune response may be mediated by a T-helper (Th1) subset of T-cells producing the cytokines interleukin-2 (IL-2) and interferon-gamma. These studies also suggest that the diabetes-protective effects of administering microbial agents, adjuvants, and a beta-cell autoantigen (GAD65 [glutamic acid decarboxylase]) may result from activati of a Th2 subset of T-cells that produce the cytokines IL-4 and IL-10 and consequently downregulate the Th1-cell-mediated autoimmune response. Th clinical implication of these findings is that the autoimmune response leadin to islet beta-cell destruction and IDDM may be amenable to prevention or suppression by therapeutic interventions aimed at stimulating the host's own immunoregulatory mechanisms.

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